

SCREENING-LEVEL HAZARD CHARACTERIZATION

SPONSORED CHEMICAL

3 and 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde (CASRN 130066-44-3)

The High Production Volume (HPV) Challenge Program¹ was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to “SIDS” (Screening Information Data Set^{1,2}) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency’s Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance^{2,3} and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor’s responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT’s focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are

¹ U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

² U.S. EPA. HPV Challenge Program – Information Sources; <http://www.epa.gov/chemrtk/pubs/general/guidocs.htm>.

³ U.S. EPA. Risk Assessment Guidelines; <http://cfpub.epa.gov/ncea/raf/rafguid.cfm>.

presented in an international forum that involves review and endorsement by governmental authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

<p>Chemical Abstract Service Registry Number (CASRN)</p>	<p><u>Sponsored Chemical</u></p> <p>130066-44-3</p> <p><u>Supporting Chemicals</u></p> <p>107-75-5</p> <p>2111-75-3</p> <p>68039-49-6</p> <p>536-59-4</p> <p>107-74-4</p>
<p>Chemical Abstract Index Name</p>	<p><u>Sponsored Chemical</u></p> <p>3-Cyclohexene-1-carboxaldehyde, 3(and 4)-(4-hydroxy-4-methylpentyl)-</p> <p><u>Supporting Chemicals</u></p> <p>Octanal, 7-hydroxy-3,7-dimethyl-</p> <p>1-Cyclohexene-1-carboxaldehyde, 4-(1-methylethenyl)-</p> <p>3-Cyclohexene-1-carboxaldehyde, 2,4-dimethyl-</p> <p>1-Cyclohexene-1-methanol, 4-(1-methylethenyl)-</p> <p>1,7-Octanediol, 3,7-dimethyl-</p>
<p>Structural Formula</p>	<p>See Section 1</p>
<p style="text-align: center;">Summary</p> <p>CASRN 130066-44-3 is a colorless viscous liquid with high water solubility and moderate vapor pressure. It is a mixture of two isomers, CASRN 31906-04-4 and CASRN 51414-25-6, in an approximate 70:30 ratio. CASRN 130066-44-3, as well as CASRN 31906-04-4 and CASRN 51414-25-6, is expected to have high mobility in soil. Volatilization is considered low based on the Henry's Law constants of the isomers. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is rapid. CASRN 130066-44-3 and its two isomers are expected to have low persistence (P1) and low bioaccumulation potential (B1).</p>	

The acute oral toxicity of CASRN 130066-44-3 in rats is low. No deaths were reported when rats were exposed to CASRN 130066-44-3 in a saturated vapor for 6 hours and observed for 14 days (vapor concentration not given). The acute dermal toxicity of CASRN 130066-44-3 in rabbits is low. CASRN 130066-44-3 is a skin sensitizer. A 28-day oral repeated dose toxicity study of CASRN 130066-44-3 in rats showed possible signs of liver toxicity at 150 mg/kg-bw/day; the NOAEL is 15 mg/kg-bw/day. In two 13-week subchronic inhalation toxicity studies in rats and hamsters respectively, the supporting chemical, CASRN 107-75-5, showed no effects at 0.000211 mg/L, the highest dose tested. A one-generation reproductive toxicity study and a companion follow-up study with CASRN 130066-44 showed mortality and adverse clinical signs, and changes in serum chemistry parameters and body weight in the dams at 500 mg/kg-bw/day; the NOAEL for maternal toxicity is 100 mg/kg-bw/day. Signs of developmental toxicity consisted of skin peeling in the pups at 100 mg/kg-bw/day; the NOAEL for developmental toxicity is 25 mg/kg-bw/day. Data regarding reproductive toxicity were not available from these studies. CASRN 130066-44-3 was not mutagenic *in vitro* in bacterial reverse mutation assays. CASRN 130066-44-3 did not induce chromosomal aberrations *in vitro* in a mammalian chromosomal aberration test. CASRN 130066-44-3 did not induce chromosomal aberrations *in vivo* in mammalian erythrocyte micronucleus tests. No evidence of carcinogenicity was reported in a 2-year feeding study in rats with the supporting chemical CASRN 107-75-5.

For CASRN 130066-44-3, the measured 96-hour LC₅₀ for fish is 11.8 mg/L. The 48-hr EC₅₀ for aquatic invertebrates was estimated by ECOSAR (v. 1.00a) to be 2.78 mg/L. The measured 72-hour EC_{50s} for aquatic plants are 25.5 and 13.8 mg/L for growth rate and biomass, respectively.

Acute toxicity to aquatic invertebrates is identified as data gap under the HPV Challenge Program.

Reproductive toxicity was identified as a data gap under the HPV Challenge Program.

The sponsor, The Flavor and Fragrance High Production Volume Consortia (FFHPVC) Alicyclic Primary Alcohol/Aldehyde/Carboxylic Acid Consortium, submitted a Test Plan and Robust Summaries to EPA for the mixture, 3 and 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde (HMPCC) (CASRN 31906-04-4; 9th CI name: 3-cyclohexene-1-carboxaldehyde, 4-(4-hydroxy-4-methylpentyl)-) on December 3, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on February, 25, 2003 (<http://www.epa.gov/chemrtk/pubs/summaries/hmpcc/c14297tc.htm>). EPA comments on the original submission were posted to the website on July, 2, 2003. Public comments were also received and posted to the website. EPA received a Revised Test Plan and Revised Robust Summary Jan. 30, 2008. (NOTE: The submitter used the CASRN 31906-04-4 for the 4-isomer (9th CI name: 3-cyclohexene-1-carboxaldehyde, 4-(4-hydroxy-4-methylpentyl)-) to designate the sponsored mixture, as this was the CASRN EPA supplied on its list of HPV substances available for sponsorship. The correct CASRN that is assigned for a 30:70 mixture of the 3 and 4-(4-hydroxy-4-methylpentenyl)-3-cyclohexene-1-carboxyaldehyde isomers is 130066-44-3. This CASRN will be used for the 30:70 mixture in this document.)

Justification for Supporting Chemicals

The sponsored chemical, (HMPCC) (CASRN 130066-44-3), exists as a 70:30 mixture of the 4- and 3-(4-hydroxy-4-methylpentenyl)-3-cyclohexene-1-carboxyaldehyde isomers. The sponsor submitted data for several supporting chemicals: 7-hydroxycitronellal (CASRN 107-75-5); 4-isopropenyl-1-cyclohexene-1-carboxaldehyde (CASRN 2111-75-3); 2,4-dimethyl-3-cyclohexenecarboxaldehyde (CASRN 68039-49-6); 4-isopropenyl-1-cyclohexenecarbinol (CASRN 536-59-4) and 7-hydroxycitronellol (CASRN 107-74-4). The sponsor stated that the structures of HMPCC and 7-hydroxycitronellal both contain an aldehyde group and a dimethyl substituted tertiary alcohol at either end of an 8 – 10 carbon chain. For the repeated-dose toxicity endpoint, EPA indicated that the use of supporting chemicals is justified by the metabolism data provided the test plan showing relatively rapid absorption of related substances and rapid excretion of metabolites. For the acute and genetic toxicity endpoints, data for the supporting chemicals are considered adequate as the data supplement existing data for the sponsored substance.

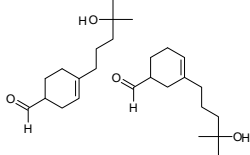
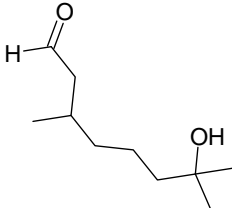
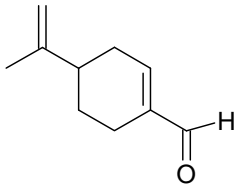
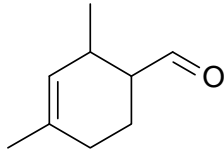
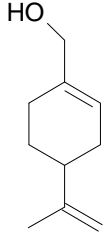
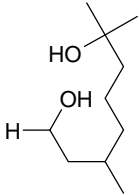
1. Chemical Identity

1.1. Identification and Purity

The following description is taken from the 2008 Test Plan, Robust Summary:

The chemical structure of CASRN 130066-44-3 features an aldehyde function and a dimethyl substituted tertiary alcohol located at either end of a carbon chain. Due to the method of preparation, CASRN 130066-44-3 exists as a 70:30 mixture of 4- and 3-(4-hydroxy-4-methylpentenyl)-3-cyclohexene-1-carboxyaldehyde isomers. One isomer (CASRN 31906-04-4), making up 70% of the mixture, is named 3-Cyclohexene-1-carboxaldehyde, 4-(4-hydroxy-4-methylpentyl)-. The other isomer (CASRN 51414-25-6), making up 30% of the mixture is named 3-Cyclohexene-1-carboxaldehyde, 3-(4-hydroxy-4-methylpentyl)-.

Test substance CASRN 130066-44-3 purity, when noted in the Robust Summaries, is given as >88%. The chemical structures are summarized in Table 1.

Table 1: Sponsored and Supporting Chemical Structures		
Chemical Abstract Index Name	CASRN	Structure
Sponsored Chemical		
3-Cyclohexene-1-carboxaldehyde, 3(and 4)-(4-hydroxy-4-methylpentyl)-	130066-44-3*	
Supporting chemicals		
Octanal, 7-hydroxy-3,7-dimethyl-	107-75-5	
1-Cyclohexene-1-carboxaldehyde, 4-(1-methylethenyl)-	2111-75-3	
3-Cyclohexene-1-carboxaldehyde, 2,4-dimethyl	68039-49-6	
1-Cyclohexene-1-methanol, 4-(1-methylethenyl)-	536-59-4	
1,7-Octanediol, 3,7-dimethyl-	107-74-4	

* The submitter used CASRN 31906-04-4 to designate this mixture.

1.2. Physical-Chemical Properties

The physical-chemical properties of CASRN 130066-44-3 and the individual isomers are summarized in Table 2. CASRN 130066-44-3 is a colorless viscous liquid with high water solubility and moderate vapor pressure.

Table 2. Physical-Chemical Properties of 3-Cyclohexene-1-carboxaldehyde, 3 and 4-(4-hydroxy-4-methylpentyl)- and the individual isomers¹			
Property	3-Cyclohexene-1-carboxaldehyde, 3 and 4-(4-hydroxy-4-methylpentyl)-	3-Cyclohexene-1-carboxaldehyde, 4-(4-hydroxy-4-methylpentyl)-	3-Cyclohexene-1-carboxaldehyde, 3-(4-hydroxy-4-methylpentyl)-
CASRN	130066-44-3	31906-04-4	51414-25-6
Molecular Weight	210.32	210.32	210.32
Physical State	Colorless viscous liquid	Colorless viscous liquid	Colorless viscous liquid
Melting Point	No measured data. Liquid	-30°C (measured) ²	No measured data. Liquid
Boiling Point	120-122°C at 1 mm Hg (measured); 308 °C (estimated) ³	318.7°C (measured) ⁴	307°C (estimated) ⁵
Vapor Pressure	0.0012 mm Hg at 25°C (estimated from reduced boiling point) ³	8.6×10 ⁻⁵ Hg at 25°C (estimated) ⁵ ; 7.4×10 ⁻⁴ Hg at 25°C (estimated) ³	8.6×10 ⁻⁵ mm Hg at 25°C (estimated) ⁵
Water Solubility	6,100 mg/L (measured data from CASRN 31906-04-4) ²	6,100 mg/L at 25°C (measured) ²	6,100 mg/L (measured data from CASRN 31906-04-4) ²
Dissociation Constant (pK _a)	Not applicable		
Henry's Law Constant	1.9×10 ⁻⁹ atm-m ³ /mole (estimated from CASRN 31906-04-4 and CASRN 51414-25-6) ⁵	1.9×10 ⁻⁹ atm-m ³ /mole (estimated) ⁵	1.9×10 ⁻⁹ atm-m ³ /mole (estimated) ⁵
Log K _{ow}	2.1 (measured) ^{1,6}	2.1 (measured) ^{1,6}	2.1 (measured) ^{1,6}

¹ Flavor and Fragrance High Production Volume Consortia. The Alicyclic Aldehyde Consortium. January 30, 2008. Final Revised Test Plan and Robust Summary for HMPCC. Available from: <http://www.epa.gov/chemrtk/pubs/summaries/hmpcc/c14297tc.htm> as of December 19, 2009.

² SRC. 2009. The Physical Properties Database (PHYSPROP). SRC: Syracuse, NY. Available from: <http://www.srcinc.com/what-we-do/free-demos.aspx> as of December 19, 2009.

³ NOMO5. 1987. Programs to Enhance PC-Gems Estimates of Physical Properties for Organic Compounds. The Mitre Corp.

⁴ Beilstein Database search. The Procter and Gamble Company Patent: US2007/280976, 2007.

⁵ U.S. EPA. 2009. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available from: <http://www.epa.gov/opptintr/exposure/pubs/episuitedi.htm> as of December 19, 2009.

⁶ Measured for a mixture consisting of 22% 3-Cyclohexene-1-carboxaldehyde, 3-(4-hydroxy-4-methylpentyl)-, and 75% 3-Cyclohexene-1-carboxaldehyde, 4-(4-hydroxy-4-methylpentyl)-.

2. General Information on Exposure

2.1. Production Volume and Exposure

According to the 2006 IUR submissions, CASRN 31906-04-4 had aggregated production and/or import volume(s) in the United States between 500,000 pounds and 1 million pounds

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical are odor agents. Commercial and consumer uses include soaps and detergents and other.

2.2. Environmental Exposure and Fate

The environmental fate properties are provided in Table 3. CASRN 130066-44-3, as well as its individual isomers, is expected to have high mobility in soil. A mixture consisting of >98% CASRN 51414-25-6 and CASRN 31906-04-4 at unspecified ratios, did not meet the criteria for readily biodegradable using a manometric respirometry test (OECD 301F), but was extensively biodegraded over the course of the 28 day incubation period. A mixture consisting of 22% CASRN 51414-25-6; and 76% CASRN 31906-04-4 degraded 41% over 28 days using a modified Sturm test (OECD 301B). CASRN 31906-04-4 was readily biodegradable using a modified MITI test (OECD 301C). Volatilization is considered low based on the Henry's Law constant of the individual isomers. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is rapid. CASRN 130066-44-3 and its two isomers are expected to have low persistence (P1) and low bioaccumulation potential (B1).

Table 3. Environmental Fate Characteristics of 3-Cyclohexene-1-carboxaldehyde, 3 and 4-(4-hydroxy-4-methylpentyl)- and the individual isomers¹			
Property	3-Cyclohexene-1-carboxaldehyde, 3 and 4-(4-hydroxy-4-methylpentyl)-	3-Cyclohexene-1-carboxaldehyde, 4-(4-hydroxy-4-methylpentyl)-	3-Cyclohexene-1-carboxaldehyde, 3-(4-hydroxy-4-methylpentyl)-
CASRN	130066-44-3	31906-04-4	51414-25-6
Photodegradation Half-life	1 hour (estimated from CASRN 31906-04-4 and CASRN 51414-25-6)	1 hour (estimated)	1 hour (estimated)
Hydrolysis Half-life	Stable under environmental conditions		
Biodegradation	62% in 28 days (not readily biodegradable); 41.2% in 28 days (not readily biodegradable)	66% in 28 days (readily biodegradable) ²	No data for the pure isomer.
Bioaccumulation Factor	BAF = 12 (estimated using measured log K_{ow} of 2.1) ³	BAF = 12 (estimated using measured log K_{ow} of 2.1) ³	BAF = 12 (estimated using measured log K_{ow} of 2.1) ³
Log K_{oc}	1.3 (estimated from CASRN 31906-04-4 and CASRN 51414-25-6) ³	1.3 (estimated) ³	1.3 (estimated) ³
Fugacity (Level III Model) ³			
Air (%)	<0.1	<0.1	<0.1
Water (%)	31.6	31.6	31.6
Soil (%)	68.3	68.3	68.3
Sediment (%)	0.1	0.1	0.1
Persistence ⁴	P1 (low)	P1 (low)	P1 (low)
Bioaccumulation ⁴	B1 (low)	B1 (low)	B1 (low)

¹ Flavor and Fragrance High Production Volume Consortia. The Alicyclic Aldehyde Consortium. January 30, 2008. Final Revised Test Plan and Robust Summary for HMPCC. Available from: <http://www.epa.gov/chemrtk/pubs/summaries/hmpcc/c14297tc.htm> as of December 19, 2009.

² National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. Available from: http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html as of December 19, 2009.

³ U.S. EPA. 2009. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available from: <http://www.epa.gov/opptintr/exposure/pubs/episuitedi.htm> as of December 19, 2009.

⁴ Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

3. Human Health Hazard

A summary of health effects data submitted for SIDS endpoints is provided in Table 4.

Acute Oral Toxicity

HMPCC (CASRN 130066-44-3)

(1) Rats (10/sex/dose) were administered HMPCC via oral gavage at 5000 mg/kg-bw and observed for 14 days. Two deaths occurred on day 1.

LD₅₀ > 5000 mg/kg-bw

(2) Sprague-Dawley rats (5/sex/dose) were administered a single dose of HMPCC via oral gavage at 4.0, 4.5, 5.0, 5.5 and 6.0 mL/kg-bw (~ 3980, 4480, 4980, 5470 and 5970 mg/kg-bw) and observed for up to 14 days. Mortality of all dose groups was seen (3/10 at 4.0 ml/kg bw; 3/10 at 4.5 ml/kg bw; 4/10 at 5.0 ml/kg bw; 4/10 at 5.5 ml/kg bw; and 5/10 at 6.0 ml/kg bw).

LD₅₀ > 5000 mg/kg-bw

(3) Rats (5/sex/dose) were administered a single dose of HMPCC via oral gavage at 2.0, 4.0, 8.0 and 16.0 mL/kg-bw (~ 1990, 3980, 7960 and 15,920 mg/kg-bw) and observed for up to 14 days. Five female rats also were administered 1.0 mL/kg-bw (~995 mg/kg-bw). Mortality in females was seen in the four highest dose groups (1/5 at 2.0 ml/kg bw; 3/5 at 4.0 ml/kg bw; 5/5 at 8.0 ml/kg bw; 2/2 at 16ml/kg bw), while mortality in males was seen in the two highest dose groups (3/5 at 8.0 ml/kg bw; and 5/5 at 16.0 ml/kg bw).

LD₅₀ (males) 7.46 mL/kg-bw (~ 7422 mg/kg-bw)

LD₅₀ (females) 3.25 mL/kg-bw (~ 3233 mg/kg-bw)

7-Hydroxycitronellal (CASRN 107-75-5, supporting chemical)

Rats (10/sex/dose) were administered 7-hydroxycitronellal at 5000 mg/kg-bw and observed for 14 days. Two deaths (1/10 on day 7 and 1/10 on day 11) occurred during the course of the study. No other information was provided.

LD₅₀ > 5000 mg/kg-bw

Acute Inhalation Toxicity

HMPCC (CASRN 130066-44-3)

Rats (5/sex/group) were exposed to HMPCC in a saturated vapor for 6 hours and observed for 14 days (vapor concentration not given). No deaths occurred.

The lethal concentration (LC₅₀) was not reported.

Acute Dermal Toxicity

HMPCC (CASRN 130066-44-3)

(1) Rabbits (10/sex/dose) were administered HMPCC via the dermal route at 5000 mg/kg-bw (conditions and exposure period not provided) and were observed for 14 days. Two deaths occurred during the course of the study, one on day 7 and one on day 13.

LD₅₀ > 5000 mg/kg-bw

(2) Rabbits (5/sex/dose) were administered HMPCC via the dermal route at 4.0, 8.0 and 16.0 mL/kg-bw/day (~ 3980, 7960 and 15,920 mg/kg-bw/day, conditions and exposure period not provided) and observed for 14 days. Mortality was observed in the two highest dose groups of males and females (3/10 animals at 8.0 ml/kg bw and 6/10 at 16 ml/kg bw).

LD₅₀ (males) 11.3 mL/kg-bw (~ 11,243 mg/kg-bw)

LD₅₀ (females) 11.5 mL/kg-bw (~ 13,433 mg/kg-bw)

7-Hydroxycitronellal (CASRN 107-75-5, supporting chemical)

Rabbits (2/sex/dose) were administered 7-hydroxycitronellal via the dermal route at 2000 mg/kg-bw (conditions and exposure period not provided) and observed for 14 days. No mortality occurred. No other information was provided.

LD₅₀ > 2000 mg/kg-bw

Repeated-Dose Toxicity

HMPCC (CASRN 130066-44-3)

Sprague-Dawley rats (5/sex/dose) were administered HMPCC in Arachis oil BP via oral gavage at 15, 150, and 1000 mg/kg-bw/day for 28 consecutive days. At 1000 mg/kg-bw/day, clinical signs due to treatment included increased salivation and respiratory pattern changes. Animals of either sex showed an increase in plasma enzymes, albumin and albumin/globulin ratio. In addition males also showed a reduction in plasma cholesterol, total protein and glucose. Animals of either sex showed an increase (statistical significance not mentioned) in absolute and relative liver weight. An increase in absolute and relative kidney weights, compared with controls, was reported in males. Histopathology revealed centrilobular or generalized hepatocyte enlargement, frequently with associated focal centrilobular inflammatory cell infiltrates for animals of either sex. At 150 mg/kg/day, an increase in absolute and relative liver weight were seen in males, with hepatocyte enlargement observed in 3/5 males.

LOAEL= 150 mg/kg-bw/day (based on possible signs of liver toxicity such as changes in absolute and relative weight and histopathology)

NOAEL = 15 mg/kg-bw/day

4-Isopropenyl-1-Cyclohexenecarbinol (CASRN 536-59-4, supporting chemical)

Fischer F344 rats (10/sex/dose) were administered 4-isopropenyl-1-cyclohexenecarbinol via oral gavage at 40, 120 or 400 mg/kg-bw/day daily for 90 days. No mortalities or clinical signs of toxicity were reported. A significant decrease in body weight was noted in the high-dose group of males. No treatment-related effects on hematology or clinical chemistry parameters were noted. Absolute kidney, liver, and lung weights were increased in high-dose females, but there were no histopathology changes in these organs.

LOAEL= 400 mg/kg-bw/day (based on decreased body weight in males)

NOAEL = 120 mg/kg-bw/day

7-Hydroxycitronellal (CASRN 107-75-5, supporting chemical)

(1) Rats were fed diets containing 7-hydroxycitronellal at 0.1% (10/sex/dose) or 0.5% (20/sex/dose) (~ 50 and 250 mg/kg-bw/day) daily for 2 years. No adverse effects were noted for gross or microscopic examination of the liver, heart, pancreas, adrenals, spleen or brain. No

information was provided regarding body weight changes or hematology or clinical chemistry parameters.

NOAEL ~ 250 mg/kg-bw/day (highest dose tested)

(2) Female CD rats (12/group) were exposed to an aerosol mixture containing 7-hydroxycitronellal at a concentration of 0.000211 mg/L for 4 hours/day, 5 days/week for 13 weeks. No toxicologically relevant effects were noted for animal survival, behavior, body weights or weight gains, organ weights or hematology, clinical chemistry or urinalysis parameters. No gross pathological or histopathological findings (trachea, lungs, adrenals, brain, esophagus, heart, kidneys, liver pancreas, spleen, sternum, testes, uterus and bone marrow taken from the femur) were observed.

NOAEL = 0.000211 mg/L (highest dose tested)

(3) Female Syrian golden hamsters (12/group) were exposed to an aerosol mixture containing 7-hydroxycitronellal at a concentration of 0.000211 mg/L for 4 hours/day, 5 days/week for 13 weeks. No toxicologically relevant effects were provided for animal survival, behavior, body weights or weight gains, organ weights or hematology, clinical chemistry or urinalysis parameters. No gross pathological or histopathological findings (trachea, lungs, adrenals, brain, esophagus, heart, kidneys, liver pancreas, spleen, sternum, testes, uterus and bone marrow taken from the femur) were observed.

NOAEL = 0.000211 mg/L (highest dose tested)

Reproductive/Developmental Toxicity

HMPCC (CASRN 130066-44-3; Sponsored Chemical)

(1) In a one-generation reproductive toxicity study (OECD TG 415), four groups of 24 Sprague-Dawley rats were administered HMPCC via gavage to 0, 25, 100 and 500 mg/kg-bw/day prior to and during mating, and continuing through gestation and lactation. Pregnant females were allowed to give birth and maintain their offspring until Day 21 post partum at which time all surviving females and offspring were sacrificed. A NOAEL of 100 mg/kg-bw/day for maternal toxicity was reported in the Robust Summary, but the actual toxic effects and details regarding statistical significance or dose-response analysis were not specified. Likewise, a NOAEL for developmental and reproductive toxicity was identified in the Robust Summary as 25 mg/kg-bw/day, but only skin sloughing in pups was reported, without any further details other than, "skin sloughing occurred at the two highest dose levels several days after birth and, after shedding, the pups appeared normal". A footnote in the Robust Summary for this study indicated there were pup deaths at the highest dose, but again, no other information was provided. No information was reported for reproductive toxicity. Although the Robust Summary for this study lacks sufficient detail to adequately determine NOAELs/LOAELs, these can be inferred from the current study in combination with that summarized in (2) below.

NOAEL (maternal toxicity) = 100 mg/kg-bw/day

LOAEL (maternal toxicity) = 500 mg/kg-bw/day (based on mortality and adverse clinical signs, and changes in serum chemistry parameters and body weight)

NOAEL (developmental toxicity) = 25 mg/kg-bw/day

LOAEL (developmental toxicity) = 100 mg/kg-bw/day (based on skin sloughing in pups)

NOAEL/LOAEL (reproductive toxicity) = undetermined (based on lack of information reported in the Robust Summary for this endpoint)

(2) A follow-up study was conducted to determine whether the effects observed in the offspring in the one-generation toxicity study were related to the test material and if so, whether they were a result of prenatal or postnatal exposures. In this study, six groups of pregnant Sprague-Dawley rats (5-10 per group) were administered HMPCC via gavage either during gestation only (days 0-21, 0-14, or 0-24), gestation and lactation, or lactation only with 0 and 500 mg/kg-bw/day. The 500 mg/kg-bw/day dose was selected because it was the dosage at which effects were observed in both dams and offspring in the one-generation reproductive toxicity study. Clinical signs of toxicity, body weights, food consumption, fertility parameters, litter sizes, pup viability at birth and maternal behavior were assessed. Mortality, adverse clinical signs, increases in serum chemistry parameters, and reductions in body weight gain were reported in dams treated during gestation. Increases in liver weights and body weights, and changes in serum chemistry parameters were reported in the dams treated during lactation. Increased incidences of stillbirths and pup deaths near parturition and up to lactation day 3, significant reductions in viability and lactation indices, and in live litter sizes, as well as transient reductions in pup weight and in flaking of pup skin with relatively few observations of skin peeling were observed in pups from dams exposed during gestation only. Significant reductions in pup viability and lactation indices, reductions in pup weights and persistent observations of skin peeling were observed in all litters from dams treated during lactation. NOAELs/LOAELs could not be determined.

Genetic Toxicity – Gene Mutation

In vitro

HMPCC (CASRN 130066-44-3)

Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* strain WP2uvrA were exposed to HMPCC at concentrations of 75, 200, 600, 1800 and 5000 µg/plate in the presence and absence of metabolic activation. Positive controls were used and appeared to produce an appropriate response. No precipitate was observed. Toxicity was noted in strains TA98 and TA1537 at 5000 µg/plate. The cytotoxic concentration was 5000 µg/plate.

HMPCC was not mutagenic in this assay

2,4-Dimethyl-3-cyclohexenecarboxaldehyde (CASRN 68039-49-6, supporting chemical)

Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to 2,4-dimethyl-3-cyclohexenecarboxaldehyde at concentrations of 0.03, 0.10, 0.30, 1.0 or 3.0 mg/plate in the presence and absence of metabolic activation. Positive controls were used and produced an appropriate response. The cytotoxic concentration was 1.0 mg/plate.

2,4-Dimethyl-3-cyclohexenecarboxaldehyde was not mutagenic in this assay

In vivo

7-Hydroxycitronellal (CASRN 107-75-5, supporting chemical)

Drosophila melanogaster were administered 7-hydroxycitronellal via the diet at 37 mM. The number of sex-linked recessive lethal mutations was not increased. No information was given on whether controls were used or produced an appropriate response.

7-Hydroxycitronellal was not mutagenic in this assay

7-Hydroxycitronellol (CASRN 107-74-4, supporting chemical)

Drosophila melanogaster were administered 7-hydroxycitronellol via the diet at 10 mM. The number of sex-linked recessive lethal mutations was not increased. No information was given on whether controls were used or produced an appropriate response.

7-Hydroxycitronellol was not mutagenic in this assay

Genetic Toxicity – Chromosomal Aberrations

In vitro

HMPCC (CASRN 130066-44-3)

Chinese hamster ovary (CHO) cells were exposed to HMPCC at concentrations of 200, 400 and 600 µg/mL for 4 hours in the absence of metabolic activation, 200, 800 and 900 µg/mL for 4 hours in the presence of metabolic activation and 100, 200 and 400 µg/mL for 20 hours in the absence of metabolic activation. A preliminary toxicity assay was tested at concentrations up to 2100 µg/mL. Positive controls were used and appeared to produce an appropriate response. Structural chromosomal aberrations were noted in the presence of metabolic activation, but not in the absence of metabolic activation. Numerical chromosomal aberrations were not produced in the presence or absence of metabolic activation. The cytotoxic concentrations were ≥ 630 µg/mL at 4 hours in the absence of metabolic activation, 2100 µg/mL at 4 hours in the presence of metabolic activation and at 210 and 2100 µg/mL at 20 hours in the absence of metabolic activation.

HMPCC did not induce chromosomal aberrations in this assay.

In vivo

HMPCC (CASRN 130066-44-3)

(1) ICR mice (5/sex/dose) were administered a single dose of HMPCC in corn oil via intraperitoneal injection at 225, 450 and 900 mg/kg-bw. Mice were killed and bone marrow smears were prepared at 48 hours for vehicle and high-dose mice and at 24 hours for all other mice. Twenty additional mice (10/sex) were given the high dose (5/sex were designated as replacement animals in the event of high mortality, 5/sex were used for bone marrow collection at 48 hours) and an additional 5 mice/sex were given a corn oil vehicle and were used for bone marrow collection at 48 hours. Positive controls were used, but no indication was given whether they produced an appropriate response. Clinical signs included piloerection and lethargy in all treated mice and irregular breathing in mice at the highest dose. One female died at 900 and replaced with the designated replacements. Micronucleated polychromatic erythrocytes were not increased in mouse bone marrow.

HMPCC did not induce chromosomal aberrations in this assay.

7-Hydroxycitronellal (CASRN 107-75-5, supporting chemical)

Male and female NMRI mice (number/sex/group not provided) were administered a single dose of 7-hydroxycitronellal via intraperitoneal injection at 0, 345, 603 and 861 mg/kg-bw. At 30 hours, the mice were killed and bone marrow smears were prepared. There was no indication of whether controls were used or produced an appropriate response. Micronucleated polychromatic erythrocytes were not increased in mouse bone marrow.

7-Hydroxycitronellal did not induce chromosomal aberrations in this assay.

7-Hydroxycitronellol (CASRN 107-74-4, supporting chemical)

Male and female NMRI mice (number/sex/group not provided) were administered a single dose of 7-hydroxycitronellol via intraperitoneal injection at 0, 516, 860 and 1204 mg/kg-bw. At 30 hours, the mice were killed and bone marrow smears were prepared. There was no indication of whether positive controls were used or produced an appropriate response. Micronucleated polychromatic erythrocytes were not increased in mouse bone marrow.

7-Hydroxycitronellol did not induce chromosomal aberrations in this assay.

Additional Information

Skin Sensitization

HMPCC (CASRN 130066-44-3)

HMPCC (Lyral) tested positive in a local lymph node assay (LLNA) at a 25% concentration.

Carcinogenicity

7-Hydroxycitronellal 2 year study (CASRN 107-75-5, supporting chemical)

In a 2-year feeding study previously described, no adverse effects were noted for gross or microscopic examination of the liver, heart, pancreas, adrenals, spleen or brain.

No evidence of carcinogenicity was reported in this study.

Conclusions: The acute oral toxicity of CASRN 130066-44-3 in rats is low. No deaths were reported when rats were exposed to CASRN 130066-44-3 in a saturated vapor for 6 hours and observed for 14 days (vapor concentration not given). The acute dermal toxicity of CASRN 130066-44-3 in rabbits is low. CASRN 130066-44-3 is a skin sensitizer. A 28-day oral repeated dose toxicity study of CASRN 130066-44-3 in rats showed possible signs of liver toxicity at 150 mg/kg-bw/day; the NOAEL is 15 mg/kg-bw/day. In two 13-week subchronic inhalation toxicity studies in rats and hamsters respectively, the supporting chemical, CASRN 107-75-5, showed no effects at 0.000211 mg/L, the highest dose tested. A one-generation reproductive toxicity study and a companion follow-up study with CASRN 130066-44 showed mortality and adverse clinical signs, and changes in serum chemistry parameters and body weight in the dams at 500 mg/kg-bw/day; the NOAEL for maternal toxicity is 100 mg/kg-bw/day. Signs of developmental toxicity consisted of skin peeling in the pups at 100 mg/kg-bw/day; the NOAEL for developmental toxicity is 25 mg/kg-bw/day. Data regarding reproductive toxicity were not available from these studies. CASRN 130066-44-3 was not mutagenic *in vitro* in bacterial reverse mutation assays. CASRN 130066-44-3 did not induce chromosomal aberrations *in vitro* in a mammalian chromosomal aberration test. CASRN 130066-44-3 did not induce

chromosomal aberrations *in vivo* in mammalian erythrocyte micronucleus tests. No evidence of carcinogenicity was reported in a 2-year feeding study in rats with the supporting chemical CASRN 107-75-5.

Table 4. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Human Health Data

Endpoints	Sponsored Chemical	Supporting Chemical	Supporting Chemical	Supporting Chemical
	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde	7-Hydroxycitronellal	2,4-Dimethyl-3-cyclohexene-carboxaldehyde	7-Hydroxycitronellol
CASRN	130066-44-3*	107-75-5	68039-49-6	107-74-4
Acute Oral Toxicity LD ₅₀ (mg/kg-bw)	> 5000	> 5000	–	–
Acute Dermal Toxicity LD ₅₀ (mg/kg-bw)	> 5000	> 2000	–	–
Acute Inhalation Toxicity LC ₅₀ (mg/L)	Not Reported	–	–	–
Repeated-Dose Toxicity NOAEL/LOAEL (Oral mg/kg-bw/day)	NOAEL=15 LOAEL=150	–	–	–
Repeated-Dose Toxicity NOAEL/LOAEL (Inhalation mg/L/day)	No Data NOAEL = 0.000211 (RA)			
Rats		NOAEL = 0.000211	–	–
Hamsters		NOAEL = 0.000211		

Table 4. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Human Health Data

Endpoints	Sponsored Chemical	Supporting Chemical	Supporting Chemical	Supporting Chemical
	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde	7-Hydroxycitronellal	2,4-Dimethyl-3-cyclohexene-carboxaldehyde	7-Hydroxycitronellol
CASRN	130066-44-3*	107-75-5	68039-49-6	107-74-4
Reproductive Toxicity NOAEL/LOAEL (Oral mg/kg-bw/day)				
Maternal Toxicity	NOAEL = 100 LOAEL = 500	–	–	–
Reproductive Toxicity	NOAEL = undetermined			
Developmental Toxicity NOAEL/LOAEL (Oral mg/kg-bw/day)	NOAEL = 25 LOAEL= 100	–	–	–
Genetic Toxicity- Gene Mutation <i>In vitro</i>	Negative	–	Negative	–
Genetic Toxicity- Gene Mutation <i>In vivo</i>	No Data Negative (RA)	Negative	–	Negative

Table 4. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Human Health Data

Endpoints	Sponsored Chemical	Supporting Chemical	Supporting Chemical	Supporting Chemical
	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde	7-Hydroxycitronellal	2,4-Dimethyl-3-cyclohexene-carboxaldehyde	7-Hydroxycitronellol
Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i>	Negative	–	–	–
Genetic Toxicity – Chromosomal Aberrations <i>In vivo</i>	Negative	Negative	–	Negative
<u>Additional Information</u>				
Skin Sensitization				
Mice	Positive in LLNA at 25% concentration	–	–	–
Carcinogenicity				
Rats	Negative (RA)	Negative	–	–

– means that the endpoint was not addressed for this chemical

(RA) = read across

* The submitter used CASRN 31906-04-4 to designate this mixture.

4. Hazards to the Environment

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 5.

See environmental hazard data at <http://www.epa.gov/chemrtk/index.htm> CASRN 130066-44-3 is a volatile chemical and testing performed with nominal concentrations underestimates its toxicity. Therefore, the estimated toxicity value for aquatic invertebrates is provided below.

Acute Toxicity to Fish

Fathead minnows (*Pimephales promelas*) were exposed to CASRN 130066-44-3 at measured concentrations of 0, 8.21, 15.1, 24.3, 42.5, and 73.0 mg/L under static renewal conditions for 96 hours in a sealed vessel.

96-hr LC₅₀ = 11.8 mg/L (measured)

Acute Toxicity to Aquatic Invertebrates

A 48-hour EC₅₀ for Daphnia estimated by ECOSAR v1.00a was used to evaluate the acute toxicity of CASRN 130066-44-3.

48-hr EC₅₀ = 2.78 mg/L (estimated)

Toxicity to Aquatic Plants

Green algae (*Selenastrum capricornutum*) were exposed to CASRN 130066-44-3 at measured concentrations of 0, 5.95, 11.9, 22.9, 45.7, and 98.4 mg/L for 72 hours. Toxicity to growth rate and biomass as a 50% decrease was measured.

72-hr EC₅₀ (growth rate) = 25.4 mg/L (measured)

72-hr EC₅₀ (biomass) = 13.8 mg/L (measured)

Conclusion: For CASRN 130066-44-3, the measured 96-hour LC₅₀ for fish is 11.8 mg/L. The 48-hr EC₅₀ for aquatic invertebrates was estimated by ECOSAR (v. 1.00a) to be 2.78 mg/L. The measured 72-hour EC_{50s} for aquatic plants are 25.5 and 13.8 mg/L for growth rate and biomass, respectively.

Table 5. Summary of the Screening Information Data Set as Submitted Under the U.S. HPV Challenge Program: Aquatic Toxicity Data	
Endpoints	Sponsored Chemical 3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
CASRN	130066-44-3*
Fish 96-h LC₅₀ (mg/L)	11.8
Aquatic Invertebrates 48-h EC₅₀ (mg/L)	2.78 (estimated)
Acute Toxicity Algae 96-h EC₅₀ (mg/L)	25.4 / 13.8

BOLD=measured data

* The submitter used CASRN 31906-04-4 to designate this mixture.

5. Reference

Gerberick, G.F. et al. Compilation of Historical Local Lymph Node Data for Evaluation of Skin Sensitization Alternative Methods. *Dermatitis*, Vol 16, No 4 (December), 2005: pp 157–202